



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :	A1	(11) International Publication Number:	WO 98/21212
C07D 503/02, A61K 31/42		(43) International Publication Date:	22 May 1998 (22.05.98)

(21) International Application Number:	PCT/EP97/06263	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(22) International Filing Date:	10 November 1997 (10.11.97)	
(30) Priority Data:	96203117.5 11 November 1996 (11.11.96) EP	
	(34) Countries for which the regional or international application was filed:	NL et al.
(71) Applicant (for all designated States except US):	GIST-BROCADES B.V. [NL/NL]; Wateringseweg 1, P.O. Box 1, NL-2600 MA Delft (NL).	
(72) Inventors; and		Published
(75) Inventors/Applicants (for US only):	BOOIJ, Johannes [NL/NL]; Bos en Duinplein 10, NL-2061 VS Bloemendaal (NL). VAN DEN HEUVEL, Antonius [NL/NL]; Brinckerinkstraat 30, NL-2531 VD Den Haag (NL).	With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.
(74) Agents:	VISSEER-LUIRINK, Gesina et al.; Gist-Brocades N.V., Patents and Trademarks Dept., Wateringseweg 1, P.O. Box 1, NL-2600 MA Delft (NL).	

(54) Title: PROCESS FOR THE PREPARATION OF SALTS AND ESTERS OF CLAVULANIC ACID

(57) Abstract

An improved process for the preparation of pharmaceutically acceptable alkali metal salts or esters of clavulanic acid has been provided for. Furthermore, also potassium clavulanate with an extremely low amine content and pharmaceutical compositions comprising the same have been provided for.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

PROCESS FOR THE PREPARATION OF SALTS AND ESTERS
OF CLAVULANIC ACID

5 The present invention relates to a process for the preparation of pharmaceutically acceptable alkali metal salts and esters of clavulanic acid, especially potassium clavulanate.

Clavulanic acid and its alkali metal salts and esters are β -lactamase inhibitors, able to enhance the effectiveness of 10 penicillins and cephalosporins.

Clavulanic acid is normally prepared by the fermentation of a microorganism which produces clavulanic acid as for instance Streptomyces strains such as Streptomyces clavuligerus. The resulting aqueous broth is normally subjected to 15 conventional purification and concentration processes, such as disclosed in GB-1508977.

EP-A-26044 discloses the use of the tertiary butylamine salt of clavulanic acid as an useful intermediate in the preparation of clavulanic acid. Other amine salts of clavulanic 20 acid are disclosed in for example WO 93/25557, WO 94/22873, EP-A-0387178, EP-A-562583, WO 96/26944 and WO 96/20199. In the present application also diamino ethers as disclosed in the latter application are considered as amines. All these cited references are incorporated in the present application by 25 reference.

The aim of this invention is to prepare clavulanic acid and its pharmaceutically acceptable salts, such as potassium, wherein the desired substance is obtained in a high yield and of high purity.

30 A lot of process improvements were surprisingly found. First of all, whole broth extraction appears to be an advantageous alternative for removing solids from the fermentation broth. A further improvement relates to the application of an amine which forms with clavulanic acid an amine clavulanate, 35 which sticks to the walls in the normally applied ethylacetate /acetone solution. The addition of a water miscible organic

- 2 -

solvent like an alcohol, preferably absolute alcohol, avoids the tendency to stick to the walls of the diamine crystals of the crystallising vessel which results in a yield loss. Furthermore, it appears to be possible to influence the crystal morphology of the end product by regulating the amount of water added during the crystallisation stage.

According to the present invention a process for the preparation of a pharmaceutically acceptable salt or ester of clavulanic acid has been provided comprising one or more of 10 the following steps:

- fermentation of a clavulanic producing microorganism;
- acidifying the clavulanic acid containing broth;
- optional addition of a small amount of a water miscible solvent;
- extraction of the acidified clavulanic acid containing broth with a water immiscible organic solvent;
- concentration of the clavulanic acid containing water immiscible organic solution by evaporation;
- purification of the concentrated clavulanic acid solution by adsorption;
- filtration of the clavulanic acid solution;
- optional addition of one or more water miscible organic solvent(s);
- addition of an amine, optionally together with a water miscible solvent, to prepare a clavulanate salt of said amine;
- optional recrystallization of the clavulanate salt of amine formed;
- conversion into purified clavulanic acid by acidifying or into a pharmaceutically acceptable salt or ester clavulanate by adding a source of the corresponding salt or ester;
- separation of the pharmaceutically acceptable salt or ester clavulanate from the solution.

35 This applies for instance to the application of amines especially of N,N,N',N'-tetramethylethylenediamine, 1,3-

- 3 -

bis(di-methylamino)-2-propanol, t-butylamine, t-octylamine, benzhydrylamine and bis (2-(dimethyl-amino)ethyl)ether.

In almost all prior art processes it is emphasized that it should be necessary to remove any of the suspended solids 5 prior to solvent extraction. Although filtration or ultrafiltration does give favourable results, it turns out that whole broth extraction does give a comparable end result in terms of yield and purity of the end product. An important advantage of leaving out the filtration step is of course a 10 larger process efficiency by leaving out a process step. The possible difficulties of broth instability and emulsion formation can be met by adding a small (up to about 25% of the total volume of the fermentation broth) amount of solvent such as a water miscible ketone or alcohol and/or pH adjustment to 15 denature proteins in the broth and/or addition of a suitable demulsifier and therefore to improve the whole broth extraction performance.

During the crystallisation stage of the amine clavulanate it has been found advantageous to add a small amount of an 20 alcohol like absolute ethanol to the mixture comprising clavulanic acid and the extracting solvent, preferably ethylacetate and the crystallising solvent, preferably acetone. In a preferred embodiment, the alcohol is added before or simultaneously with the amine. The application of this three component mixture of solvent diminishes the exhibition of the crystals to stick to the walls resulting in a loss of yield and it also leads surprisingly to an enhancement of the purity 25 and general quality characteristics. All ways of addition of the amine to the mixture comprising clavulanic acid result then in favourable crystallization results, for instance 30 besides addition of the amine to the mixture comprising clavulanic acid both simultaneous addition of the amine and the clavulanic acid mixture to a reaction vessel and the addition of clavulanic acid mixture to the amine. Furthermore, 35 recrystallisation can optionally be applied by treating the aqueous solution of amine clavulanate, either neat or partly

- 4 -

diluted with solvent, with charcoal and then sterile filtering the resulting solution prior to sterile crystallisation.

During the formation of the potassium clavulanate it has been found advantageous to form the same by slurring the 5 amine salt in a solvent, preferably a water miscible ketone or alcohol and then adding a potassium source, preferably potassium ethyl hexanoate in a solvent, also preferably a water miscible ketone or alcohol. Use of a slurry system reduces significantly the amount of solvent required which 10 reduces costs and increases the yield of the endproduct.

Furthermore, it has been found advantageous to add a small amount of water to the (slurry) solvent. Surprisingly it has been found that by doing this it is possible to influence the crystal morphology of the final product. Thus it is possible 15 to obtain crystals which can be washed more readily and which have improved filtration and drying characteristics. In this way it is possible to form either rosette or needle formed crystals, preferably a cluster of needles formed crystals.

Furthermore, especially in case as amine the bis(2-(dimethylamino)ethyl)ether is applied the residual amine in the 20 endproduct is extremely low, lower than 0.05% w/w, preferably lower than 0.02% w/w appears to be possible, viz. ten times lower than the level of tertiary butylamine permitted by the British Pharmacopoeia. A low amine content in the amine 25 clavulanate intermediate is desirable since it results in a more stable endproduct. Therefore, it is really advantageous to apply potassium clavulanate, prepared in this way, in a pharmaceutical composition comprising potassium clavulanate and amoxycillin trihydrate.

30 The following examples are given for illustration purposes only.

- 5 -

Examples

Example 1

5 Whole broth extraction of a clavulanic acid containing broth

Broth resulting from a fermentation with Streptomyces clavuligerus, (3.5 l, containing 13.3 g of clavulanic acid) was cooled to 2 °C. This broth was added to 10.5 l ethylacetate at 1-3 °C while stirring. After addition of the broth, the pH of the mixture was adjusted to pH=1.6 with the aid of 3 M sulphuric acid. The mixture was rested to settle for 5 minutes, and the layers were separated. 9.25 l of ethylacetate layer was collected, containing 7.5 g of clavulanic acid.

15

Example 2

Evaporation of clavulanic acid containing ethyl acetate solution

20

The ethylacetate solution (9.25 l) from the preceding example was evaporated in vacuo at 30-35 °C, using a natural circulation evaporator. A concentrated solution (0.88 l) was obtained, containing 7.5 g of clavulanic acid. This solution 25 was concentrated using a rotatory thin film evaporator (vacuum, 30-35 °C). A concentrate (0.11 l) was obtained, containing 7.4 g of clavulanic acid.

30

Example 3

Preparation of crystalline bis (2-(dimethylamino)ethyl)ether diclavulanate

Into a one litre three-necked roundbottom flask fitted 35 with a thermometer, two dropping funnels and a stirrer was placed ethanol (50 ml). The temperature was brought to 10° C and under stirring an impure solution of clavulanic acid

- 6 -

(400 ml; 32.9 g clavulanic acid/litre) in ethyl acetate and a solution of bis(2-(dimethylamino)ethyl)ether (13.5 g) in ethanol (230 ml) were added simultaneously. The temperature during the addition was maintained between 10-15° C. After the 5 addition (15-20 minutes), the mixture was stirred for one hour at 5° C. The crystals were filtered, washed twice with ethyl acetate (40 ml) and dried under vacuum at room temperature. 16 g of bis(2-(dimethylamino)ethyl)ether diclavulanate was obtained.

10

Example 4

Purification of clavulanic acid solution by treatment with charcoal

15

The concentrated ethyl acetate solution of example 2 (7.4 g of clavulanic acid in 110 ml) was subjected to a charcoal treatment. The solution was cooled to 5 °C, and charcoal (16.5 g, Norit SX Ultra) was added. The mixture was stirred 20 during two hours at 5-10 °C. Filter aid (Dicalite, 5 g) was added, and the mixture was filtered. The solid cake was washed with ethyl acetate until the volume of the collected filtrate was 185 ml.

25

Example 5

Crystallization of bis(2-(dimethylamino)ethyl)ether diclavulanate from a concentrated clavulanic acid solution in ethyl acetate

30

The following experiment was carried out in nitrogen atmosphere. Absolute ethanol (450 ml) was added to a solution of clavulanic acid in ethyl acetate (900 ml, concentration 40 g of clavulanic acid/litre). The solution was stirred, 35 cooled to 10 °C, and bis(2-(dimethylamino)ethyl)ether (35.1 ml, 0.18 moles) was added. The mixture was cooled to 3 °C, and stirred during one hour. The crystal suspension was

- 7 -

filtered, and the cake was washed with 200 ml of acetone, and again with 200 ml of acetone. The wet cake was dried in vacuum at room temperature. 45 g of bis(2-(dimethylamino)ethyl)ether diclavulanate was obtained.

5

Example 6

Crystallization of potassium clavulanate starting from bis(2-(dimethylamino)ethyl)ether diclavulanate

10

The following experiment was carried out in nitrogen atmosphere. Bis(2-(dimethylamino)ethyl)ether diclavulanate (10 g) was suspended in a mixture of acetone (300 ml) and water (6 ml). The mixture was stirred, cooled to 12 °C, and 15 a solution of potassium 2-ethylhexanoate in acetone (125 ml of a 0.34 M solution) was added in the course of 10 minutes. The mixture was cooled to 5 °C, and stirred during one hour. The crystal suspension was filtered and the cake was washed with three cake volumes acetone. The wet cake was dried in 20 vacuum at 20 °C. 8.22 g of potassium clavulanate was obtained.

Example 7

Purification of bis(2-(dimethylamino)ethyl)ether diclavulanate by recrystallization

The following experiment was carried out in nitrogen atmosphere. Bis(2-(dimethylamino)ethyl)ether diclavulanate (10 g) was dissolved in a mixture of absolute ethanol (45 ml) 30 and water (5 ml) at 20 °C. The clear solution was added to acetone (250 ml) in the course of 20 minutes while stirring the mixture at 20 °C. The mixture was cooled to 5 °C, and stirred during 30 minutes. The crystal suspension was filtered, and the cake was washed with 2 cake volumes of acetone. 35 The crystals were dried in vacuum at 20 °C. 9.44 g of bis(2-(dimethylamino)ethyl)ether diclavulanate was obtained.

- 8 -

Example 8

Crystallization of potassium clavulanate starting from bis(2-(dimethylamino)ethyl)ether diclavulanate with intermediate charcoal treatment

5

The following experiment was carried out in nitrogen atmosphere. Bis(2-(dimethylamino)ethyl)etherdiclavulanate (10 g) was dissolved in a mixture of absolute ethanol (45 ml) and water (5 ml) at 20 °C. The pH of the mixture was adjusted to 10 pH=6.5 with the aid of 2-ethylhexanoic acid. Charcoal (1 g) was added, and the mixture was stirred during 30 minutes. Filter aid was added (Dicalite, 0.3 g), and the mixture was filtered. The cake was washed with absolute ethanol (5 ml), and acetone (10 ml). The combined filtrates were added to 15 acetone (250 ml) at 10 °C. A crystal suspension was obtained. A solution of potassium 2-ethylhexanoate in acetone (125 ml of a 0.34 M solution) was added in the course of 10 minutes. The mixture was cooled to 5 °C, and stirred during one hour. The crystal suspension was filtered and the cake was washed 20 with three cake volumes of acetone. The wet cake was dried in vacuum at 20 °C. 7.56 g of potassium clavulanate clusters of needles was obtained.

5

CLAIMS

1. A process for the preparation of a pharmaceutically acceptable salt or ester of clavulanic acid comprising the following steps:

- 10 - fermentation of a clavulanic producing microorganism;
 - acidifying the clavulanic acid containing broth;
 - optional addition of a small amount of a water miscible solvent;
 - extraction of the acidified clavulanic acid containing broth with a water immiscible organic solvent;
 - 15 - concentration of the clavulanic acid containing water immiscible organic solvent by evaporation;
 - purification of the concentrated clavulanic acid solution by adsorption;
 - 20 - filtration of the clavulanic acid solution;
 - optional addition of one or more water miscible organic solvent(s);
 - addition of an amine optionally together with a water miscible solvent to prepare a clavulanate salt of said amine;
 - 25 - optional recrystallization of the clavulanate salt of amine formed;
 - conversion into purified clavulanic acid by acidifying or into a pharmaceutically acceptable salt or ester clavulanate by adding a source of the corresponding salt or ester;
 - 30 - separation of the pharmaceutically acceptable salt or ester clavulanate from the solution.
- 35 2. A process according to claim 1 wherein as amine any one of the amines N,N,N',N'-tetramethylethylenediamine, 1,3-bis(dimethylamino)-2-propanol, t-

- 10 -

butylamine, t-octylamine, benzhydrylamine and bis (2-(dimethylamino)ethyl)ether is applied.

3. A process according to anyone of the claims 1 and 2,
5 wherein solids are removed from the clavulanic acid containing
fermentation broth before extraction.

4. A process according to anyone of the claims, character-
ized by the addition of a water miscible ketone and/or
10 alcohol to the fermentation broth.

5. A process according to anyone of the claims 1 - 4,
characterized by extraction of the acidified clavulanic acid
containing broth with ethylacetate.

15 6. A process according to anyone of the claims 1 - 5,
wherein purification of the concentrated clavulanic acid sol-
ution is carried out by treatment with charcoal.

20 7. A process according to anyone of the claims 1 - 6,
characterized by the addition of the water miscible solvent
acetone to the clavulanic acid solution after the purification
and filtration steps.

25 8. A process according to anyone of the claims 1 - 7,
characterized by the addition of the water miscible solvent
ethanol to the solution comprising clavulanic acid, before or
simultaneous with the addition of the amine to prepare a
clavulanate salt of the amine.

30 9. A process according to anyone of the claims 1 - 8,
characterized by carrying out the conversion of the clavulan-
ate salt of amine into potassium clavulanate by slurring the
amine salt in a slurring solvent and adding a solution of a
35 source of potassium ions.

- 11 -

10. A process according to claim 9, characterized by adding a small amount of water to the slurrying solvent.

11. A process according to anyone of the claims 1 - 10, 5 characterized by recrystallization of said amine clavulanate in a mixture of ethanol and water, optional treatment with charcoal and crystallisation by the addition of acetone.

12. A process for the preparation of potassium clavulana- 10 te, characterized by

- fermentation of Streptomyces clavuligerus to produce clavulanic acid;
- acidifying the clavulanic acid containing broth to a pH between 1 and 3 by addition of a concentrated acid solution;
- optional removing of solids from the fermentation broth;
- optional addition of a small amount of a water miscible ketone or alcohol;
- extraction of the acidified clavulanic acid containing broth with ethylacetate;
- concentration of the clavulanic acid containing ethylacetate solution by evaporation;
- purification of said solution by treatment with charcoal;
- filtration of the resulting clavulanic acid solution;
- optional addition of acetone;
- addition of ethanol and anyone of the amines N,N,N',N'-tetramethylethyleendiamine, 1,3-bis(dimethylamino)-2-propanol, t-butylamine, t-octylamine, benzhydrylamine and bis (2-(dimethylamino)ethyl)ether;
- optional recrystallisation of the potassium clavulanate formed by dissolution of the same in a mixture of ethanol and water, optional treatment with charcoal, and crystallisation in acetone;

- 12 -

- conversion into potassium clavulanate by adding potassium ethylhexanoate;
- isolation of potassium clavulanate from the slurry.

5

13. A process according to claim 12, characterized by carrying out the conversion into potassium clavulanate by slurring the amine clavulanate in a water miscible ketone or alcohol and optionally adding a small amount of water to the
10 slurring solvent.

14. Potassium clavulanate with an amine content of lower than 0.05% w/w.

15 15. Potassium clavulanate according to claim 14 with an amine content of lower than 0.02% w/w.

16. Pharmaceutical composition comprising potassium clavulanate as defined in claim 14 or 15, and amoxycillin
20 trihydrate.

INTERNATIONAL SEARCH REPORT

Int'l. Application No
PCT/EP 97/06263

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D503/02 A61K31/42

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 594 099 A (PHARMA DEVELOPMENT LTD.) 27 April 1994 see the whole document ---	1-16
Y	WO 96 20199 A (SPURCOURT LTD.) 4 July 1996 cited in the application see the whole document ---	1-16
Y	WO 96 28452 A (LEK PHARMACEUTICAL AND CHEMICAL CO. D.D.) 19 September 1996 see the whole document ---	1-16
Y	WO 96 33197 A (LEK PHARMACEUTICAL AND CHEMICAL CO. D.D.) 24 October 1996 see the whole document ---	1-16
		-/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"Z" document member of the same patent family

1

Date of the actual completion of the international search

24 March 1998

Date of mailing of the international search report

06/04/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Chouly, J

INTERNATIONAL SEARCH REPORT

Int'l. Application No PCT/EP 97/06263
--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 25557 A (SMITHKLINE BEECHAM PLC) 23 December 1993 cited in the application see the whole document ----	1-16
Y	WO 95 23870 A (LEK.) 8 September 1995 see the whole document ----	1-16
Y	WO 94 21647 A (SMITHKLINE BEECHAM PLC) 29 September 1994 see the whole document ----	1-16
Y	WO 95 34194 A (CHONG KUN DANG CORO.) 21 December 1995 see the whole document -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/EP 97/06263

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 594099 A	27-04-94	AU 669212 B AU 4900893 A CA 2107928 A CZ 9302211 A HU 66020 A JP 6197782 A NZ 248917 A PL 300747 A SI 9300556 A ZA 9307638 A	30-05-96 05-05-94 22-04-94 18-05-94 29-08-94 19-07-94 28-08-95 16-05-94 30-06-94 05-05-94
WO 9620199 A	04-07-96	AU 4311096 A CA 2208520 A EP 0799233 A FI 972464 A NO 972946 A PL 321092 A SE 9702306 A ZA 9510880 A	19-07-96 04-07-96 08-10-97 21-08-97 23-06-97 24-11-97 25-08-97 07-08-96
WO 9628452 A	19-09-96	SI 9500074 A AU 4950496 A CA 2215038 A EP 0813536 A	31-10-96 02-10-96 19-09-96 29-12-97
WO 9633197 A	24-10-96	SI 9500134 A AU 5340196 A EP 0821687 A	31-10-96 07-11-96 04-02-98
WO 9325557 A	23-12-93	AP 471 A AP 473 A AP 474 A AT 1447 U AT 475 U AT 146180 T AT 157981 T AT 134192 T AU 681569 A AU 1471697 A AU 680099 B	06-03-96 06-03-96 06-03-96 26-05-97 27-11-95 15-12-96 15-09-97 15-02-96 28-08-97 22-05-97 17-07-97

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No

PCT/EP 97/06263

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9325557 A		AU 1473795 A	22-06-95
		AU 665159 B	14-12-95
		AU 1786595 A	06-07-95
		AU 4342793 A	04-01-94
		BG 60999 B	30-08-96
		BG 99131 A	28-08-95
		BG 61306 B	30-05-97
		BG 99639 A	29-02-96
		BG 61190 B	28-02-97
		BG 99640 A	29-02-96
		CA 2117538 A	23-12-93
		CA 2160768 A	12-12-93
		CN 1095069 A	16-11-94
		CN 1112928 A	06-12-95
		CN 1113244 A	13-12-95
		CY 1895 A	27-09-96
		CZ 9600193 A	13-08-97
		CZ 9500544 A	13-08-97
		CZ 9501254 A	12-06-96
		CZ 9402021 A	15-12-94
		CZ 9402675 A	13-08-97
		CZ 9402676 A	13-08-97
		DE 4345286 A	21-09-95
		DE 4345311 C	01-02-96
		DE 4392664 T	01-06-95
		DE 69301571 D	28-03-96
		DE 69301571 T	18-07-96
		DE 69306574 D	23-01-97
		DE 69306574 T	30-04-97
		DE 69313869 D	16-10-97
		DE 69313869 T	29-01-98
		DK 68595 A	15-06-95
		DK 140694 A	08-12-94
		EP 0644887 A	29-03-95
		EP 0699682 A	06-03-96
		EP 0672669 A	20-09-95
		EP 0672670 A	20-09-95

WO 9523870 A	08-09-95	SI 9400107 A	31-10-95
		AT 159549 T	15-11-97

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 97/06263

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9523870 A		AU 1724195 A BG 100816 A CA 2184619 A CN 1143388 A CZ 9602557 A DE 69500925 D DE 69500925 T EP 0748387 A FI 963408 A HU 74944 A JP 9504702 T NO 963628 A NZ 279958 A PL 316085 A SK 112096 A ZA 9501689 A	18-09-95 31-10-97 08-09-95 19-02-97 11-12-96 27-11-97 12-02-98 18-12-96 30-10-96 28-03-97 13-05-97 17-10-96 24-04-97 23-12-96 05-02-97 11-12-95
WO 9421647 A	29-09-94	AU 6212194 A	11-10-94
WO 9534194 A	21-12-95	AU 3579195 A EP 0827504 A ZA 9509443 A	05-01-96 11-03-98 29-05-96